INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI
SHORT ABSTRACT OF THESIS

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SHORT ABSTRACT

Homeobox (HOX) genes encode homeodomain-containing transcription factors. They play a crucial role in determining cell identity and regional specification along the anterior-posterior axis during embryonic development. Recent investigations suggest that these genes are aberrantly expressed in a variety of cancers. HOXB2, a member of the HOXB cluster of the homeobox family, is overtly expressed in various solid tumors. Using an *in-vivo* screen to identify breast tumor growth regulators in murine mammary fat pads, Boimel and co-workers recently identified HOXB2 as a tumor suppressor. However, the mechanistic underpinnings of its role in breast cancer is not understood. Given the emerging interaction of estrogen-regulated gene expression and altered HOX gene expression network in the pathophysiology of breast cancer, this study addressed the relationship between estrogen signaling and HOXB2 expression and signified the clinical significance of HOXB2. High HOXB2 expression was correlated with better survival of breast cancer patients. TCGA data revealed that HOXB2 expression was positively correlated with estrogen receptor-α (ERα), suggesting that HOXB2 may be affected by estrogen signaling. We showed that estrogen suppresses HOXB2 mRNA and protein expression in MCF-7 and T47D breast cancer cell lines. Chromatin immunoprecipitation assay confirms that estrogen-mediated suppression of HOXB2 is via ERα and is associated with increased ERα binding in the estrogen response element located in the 5' upstream of HOXB2. HOXB2 knockdown experiments showed that modulations in the expression of HOXB2 affect ERα and expression of various estrogen-regulated genes such as pS2, PR, CSTA, GRAMD4, and PCDH8. Estrogen suppresses HOXB2, and HOXB2 knockdown increased PCDH8 expression. Investigating the estrogen-mediated regulation of PCDH8 revealed that estrogen causes suppression of PCDH8 expression via ERα in MCF-7 and T47D breast cancer cells. Further, HOXB2 knockdown decreased and increased the expression of epithelial and mesenchymal markers, respectively. These results suggest that HOXB2 may be involved in epithelial-mesenchymal transition, affecting the invasion and metastasis. Taken together, the present study offers novel insights into estrogen regulation of HOXB2 in breast cancer cells and provides detailed molecular insights into ERα-mediated regulation of HOXB2. Our results suggest that HOXB2 may be a mediator in estrogen-regulated gene expression. This work provides insights into the role of HOXB2 in breast cancer and presents HOXB2 as a potential player in the estrogen-ERα and HOX gene expression network.